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Original Research

Do the MEFV gene mutations increase in patients with autosomal dominant polycystic kidney disease? Preliminary analysis

MEFV gene mutation and autosomal dominant polycystic kidney disease

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Abstract
Aim: The aim of the present study was to evaluate the frequency of MEFV gene mutations in autosomal dominant polycystic kidney disease (ADPKD) patients with abdominal pain, tenderness, fever or arthritis attacks who may have coexistence of Familial Mediterranean Fever (FMF).
Materials and Methods: Twenty-five ADPKD patients with the medical history of recurring and self-limited episodes of fever, abdominal pain, and inflammatory arthritis of one or several serous (peritoneum, pleura, pericardium, synovial or vaginal tunic of the testicle) membranes attending consecutively our nephrology, rheumatology, and gastroenterology departments were included in the study, and MEFV gene mutations were analyzed.
Results: In this study, twenty-five ADPKD patients (male/female:15/10) were included. The mean age was 43.8 years. In 8 ADPKD patients, MEFV gene mutations were determined with 9 allelic variants. We found the prevalence of total allelic MEFV variants to be the same in ADPKD patients (32%) compared with healthy Turkish subjects ($p > 0.05$). According to the Tel-Hashomer criteria, four patients with proteinuria higher than 1000 mg were diagnosed with FMF and amyloidosis by endoscopic biopsies.
Discussion: Coexistence of two common genetic and systemic disorders like ADPKD and FMF may take place . Furthermore, MEFV gene mutations may play a role in the development of FMF-related amyloidosis in ADPKD patients. Colchicine use in FMF, besides preventing the development of amyloidosis, may also prevent the development of cysts in the concurrence with ADPKD. Further large clinical studies on this subject are needed.

Keywords
Autosomal Dominant Polycystic Kidney Disease; Familial Mediterranean Fever; MEFV Gene Mutation; Colchicine; Amyloidosis

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common of the inherited renal cystic diseases resulting in a high ratio of the end-stage renal disease (ESRD) in the Turkish population [1]. Familial Mediterranean fever (FMF) is an autosomal recessive systemic autoinflammatory disease characterized by recurrent attacks of polyserositis and fever [2]. ADPKD is one of the most frequent inherited kidney disease, with a prevalence of 1/1000 [3], caused by polycystins 1 and 2, PKD1 and PKD2 gene mutations in 85% and 15% of the cases respectively [4].

PKD1 gene of ADPKD and MEVF gene are located on the same chromosome region (16p13.3), but slightly differently placed on 46 exons and 2, 10 exons respectively [4,5]. Fever and abdominal pain/tenderness in ADPKD patients are generally believed to have resulted from the renal and urinary complications. However, these symptoms also may be caused by inflammation of serous membranes due to FMF. These individuals with ADPKD may have increased frequency of MEFV gene mutation carriage in risk groups. Therefore, we aimed to evaluate the frequency of MEFV gene mutations in ADPKD patients with abdominal pain, tenderness, fever or arthritis attacks who may have coexistence of FMF.

Material and Methods

Twenty-five ADPKD patients with the medical history of recurrent and self-limited episodes of fever, abdominal pain and inflammatory arthritis of one or several serous membranes attending consecutively our nephrology, rheumatology, and gastroenterology departments were recruited into the study. Informed consent was obtained from all individual participants included in the study. In enrolled patients, the diagnosis of ADPKD was re-established based on family history (family anamnesis), clinical data, and a new ultrasound of kidneys using the criteria described by Pei et al. [6]. Unfortunately, no additional genetic profiling was performed in ADPKD patients and MEFV gene mutations were analyzed. DNA was extracted from peripheral blood leukocytes using standard protocols (Invisorb® Spin Blood Kit, STRATEC Molecular GmbH, D-13125; Berlin, Germany). Molecular analyses were performed within the framework of routine genetic testing. The presence of MEFV mutation was investigated in exons 2, 3, 5 and 10 by the multiplex-PCR reverse hybridization method. Familial Mediterranean fever was diagnosed on the basis of the Tel–Hashomer diagnostic criteria [7]. The diagnosis of amyloidosis was based on histological proof of congophilic fibrillar deposits in endoscopic biopsy specimens.

Statistical analyses

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) software, version 15.0 statistical package program (IBM Inc.; Chicago, IL, USA). Demographic and clinical variables were summarized as proportions. The Chi-square test was used for the comparison of categorical variables. A p-value <0.05 was considered as statistically significant.

Results

In this study, twenty-five ADPKD patients (male/female:15/10) were included. The mean age was 43.8 years. In 8 ADPKD patients, MEFV gene mutations were determined with 9 allelic variants. The allelic variants were heterozygous for M694V (4/50, 8%), E148Q (2/50, 4%), V726A, P369S, A744S, and compound heterozygous for M680I/M694V. According to the Tel-Hashomer criteria, four patients with proteinuria higher than 1000 mg were diagnosed with FMF and amyloidosis by endoscopic biopsies. Two of them were heterozygous for M694V, one of them was heterozygous for A744S, and one of them was compound heterozygous for M680I / M694V. Two of the 4 patients with ESRD and amyloidosis (M694V and A744S) had a successful living and cadaveric donor renal transplantations after a 5-year dialysis period at the age of 48, 59 years, respectively.

Discussion

In the current study, we found that the prevalence of total allelic MEFV variants tends to be high in ADPKD patients (32%) compared with healthy Turkish subjects ($p > 0.05$).

In the literature, a high frequency of MEFV carriers in a healthy Turkish population (20%) was reported [8].

In ADPKD and FMF, the genetic mutations are present in the same chromosome region, suggesting that these two diseases would occur together [4,5]. Özen et al. pointed out the prevalence of FMF (included Turkish patients) among four ethnic groups as high as 1/500 in a ratio which is alike to the prevalence of 1/1000 in ADPKD patients [3,9].

As a result of the disorder occurring in the synthesis of pyrin due to the MEFV gene mutation, the increase of acute inflammation can contribute to the concurrence of inflammatory diseases other than FMF. Earlier studies have reported increased frequency of Henoch-Schonlein purpura, polyarteritis nodosa, ankylosing spondylitis, Behcet disease, and inflammatory bowel diseases in FMF patients [10-11,12]. In those with negative MEFV gene mutation FMF patients, the absence of other concurrent autoimmune diseases may indicate the role of MEFV gene mutation [12].

Although there was no statistically significant increase in MEFV gene mutations in ADPKD patients compared with the healthy controls in the Turkish population, four patients were diagnosed with FMF and amyloidosis according to the Tel-Hashomer diagnostic criteria [7].

In ADPKD, usually moderate proteinuria may be seen in conjunction with renal failure, but the development of proteinuria and amyloidosis in nephrotic level is rare. The most important reason for the development of amyloidosis is chronic cyst infection [13,14].

The ADPKD phenotype displays a significant variability that is widely influenced by the affected gene. In PKD1 patients, a median age at onset of ESRD was 58 years [4], and about 2–5% of ADPKD patients present with an early and severe phenotype [15]. There may be a coexistence of these two common genetic disorders. Although it is not certain, amyloidosis in these cases may take place due to FMF or recurrent cyst infections. MEFV

gene mutations here may play a role in the development of FMF-related amyloidosis in ADPKD patients.

In this regard, MEFV gene mutations, comorbidities, and/or other urological, renal complications (like amyloidosis) may constitute the severity and early manifestation of ADPKD.

Colchicine is an effective drug used in the treatment of FMF to prevent the development of attacks and amyloidosis. Colchicine is a microtubule inhibitor, preventing cell migration, division, and polarisation. It also has anti-apoptotic, anti-proliferative and anti-inflammatory effects [16]. Many of the effects of colchicine have pathophysiologic counterpart of ADPKD, thus Solak et al. hypothesized that colchicine would be beneficial for regression and/or prevention of cyst formation in ADPKD [16]. Our study constitutes another basis for the use of colchicine in patients with ADPKD which in addition to preventing the development of cysts, may also prevent the development of amyloidosis especially in the presence of FMF.

As a conclusion, ADPKD patients may have similar symptoms with FMF like fever, tenderness, abdominal pain, loss of appetite, nausea and vomiting. In regions and ethnic groups where FMF prevalence is high, FMF symptoms and ADPKD complications should be differentiated.

Further large clinical trials are necessary to evaluate whether the coexistence of these two disorders can simply be explained as incidental or not. The clinical therapeutic effect of colchicine on cyst development in patients with ADPKD should be investigated.

Limitations of the study

A number of limitations of the study design should be acknowledged and kept in mind when evaluating the consequences. First, we did not analyze the molecular genotyping of the included participants and thus have no way to determine whether PKD1, PKD2 and/or even overlap undetermined mutations caused the genotype-phenotype correlations in ADPKD patients. Secondly, data sets of a small number of patients (there were only 25 individuals) were limited to assess the results. Finally, the etiology of amyloidosis may not certainly be determined if it is due to FMF or chronic cyst infections.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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